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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,115	01/07/2004	Timothy D. Hey	DAS-104XC1	8974

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,115	HEY ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3,9,11-13 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election without traverse of Group I, claims 1-15, in the reply filed on January 26, 2006 is acknowledged. Claims 16-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions, there being no allowable generic or linking claim. Applicants' election of the invention in which Protein A is SEQ ID NO: 34, Protein B is SEQ ID NO: 45 and Protein C is SEQ ID NO: 47 in their reply filed on October 17, 2005 is also acknowledged. No claims have been amended, canceled or added. Claims 3, 9, 11-13 and 15 are withdrawn from prosecution as being drawn to non-elected inventions. Accordingly, claims 1, 2, 4-8, 10 and 14 are examined on the merits herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-8, 10 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite that the insecticide of the claimed method includes forms of Proteins A, B and/or C that are any fragments (each of these proteins may be truncated at any position or positions) or any variants in

which any number of amino acids at any positions may be substituted by conservative amino acid changes. No such variants or truncation fragments are disclosed in the specification. Thus, one of skill in the art would have no idea which variants or fragments Applicants have in mind that they wish to include within the scope of the claimed invention. Also, one of skill in the art would have no idea which variants or fragments of the disclosed sequences have functional activity as an insecticide.

Consequently, there is no evidence that any representative species of such large and varied genera- proteins that vary from SEQ ID NOS: 34, 45 or 47 by the conservative substitution of a variable number of amino acids at a variable number of positions and proteins that are any truncation fragments of SEQ ID NOS: 34, 45 or 47- were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Because no variants or fragments of SEQ ID NOS: 34, 45 or 47 are disclosed, the claims fail to satisfy the written description requirement.

Claims 1, 2, 4-8, 10 and 14 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of controlling or inhibiting an insect by contacting the insect with a composition comprising SEQ ID NO: 34, SEQ ID NO: 45 and SEQ ID NO: 47, does not reasonably provide enablement for a method of controlling

or inhibiting an insect by contacting the insect with a composition comprising any truncation fragment or any conservatively substituted variant of any or all of SEQ ID NO: 34, SEQ ID NO: 45 or SEQ ID NO: 47. Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in

the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

The claims are very broad because they recite a method of controlling or inhibiting an insect by contacting it with a composition comprising SEQ ID NOS: 34, 45 and 47 or a composition comprising any fragment or any conservatively substituted variant of one or all of these three proteins.

2. The nature of the invention.

The invention is designed to provide a method of controlling or inhibiting insects.

3. The state of prior art.

Morgan et al. ("Sequence analysis of insecticidal genes from *Xenorhabdus nematophilus* PMFI296," Appl Environ Microbiol 67:2062-2069, 2001) disclose an insecticidal protein from *Xenorhabdus* that has 95% sequence identity to SEQ ID NO: 34 (see enclosed alignment, Result 1 from a search in the UniProt database). Ffrench-Constant et al. (US 2004/0103455, which claims priority to US 60/425,672, filed on November 12, 2002) disclose insecticidal proteins from *Photorhabdus luminescens*, SEQ ID NO: 10 and 12, that have 100% sequence identity to SEQ ID NOS: 45 and 47, respectively (see enclosed alignments, Result 1 from a search in the database of published U.S. patent applications for each protein). Duchaud et al. (WO 02/094867) disclose an insecticidal protein from *Photorhabdus luminescens* that has 92% sequence identity to SEQ ID NO: 45 (see enclosed alignment, Result 3 from a search in the Geneseq database). Kramer et al. (US 6,281,413) disclose an insecticidal protein from *Photorhabdus luminescens*, SEQ ID NO: 12, that has 91% sequence identity to SEQ ID NO: 47 (see enclosed alignment, Result 1 from a search in the database of issued U.S. patents).

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

Because it is not known how to vary the amino acid sequence of SEQ ID NOS: 34, 45 or 47 by conservatively substituting an unlimited number of amino acids so that the variant sequence retains insecticidal activity, and because it is not known which truncation fragments have insecticidal activity, the specification needs to have more detail as how to make and use the invention. Because the prior art and the instant specification do not

disclose any variants of SEQ ID NOS: 34, 45 or 47 in which one or more amino acids have been conservatively substituted and the insecticidal activity is retained, or any fragments of any of these three proteins that retain the insecticidal activity, whether or not the activity is "stand-alone," it cannot be predicted that any variants of SEQ ID NOS: 34, 45 or 47 would retain these activities.

6. The amount of guidance present.

Applicants have not provided any guidance for preparing fragments or conservatively substituted variants of SEQ ID NOS: 34, 45 or 47 that have insecticidal activity, either stand-alone activity or otherwise.

7. The existence of working examples.

The specification contains working examples showing the insecticidal activity of the claimed sequences. No variant proteins or protein fragments are used in the experiments.

8. The quantity of experimentation necessary.

To prove that a protein that is a fragment of SEQ ID NO: 34, 45 or 47, or that has the sequence of SEQ ID NO: 34, 45 or 47 in which any one or more amino acids from one or more of these three proteins is substituted as a conservative substitution, retains insecticidal activity, many experiments would have to be conducted under a wide range of conditions. In these experiments, many fragments and many variant proteins would have to be tested for insecticidal activity. The fragments and variants of SEQ ID NO: 34 would have to be tested for stand-alone activity. The fragments and variants of SEQ ID NOS: 45 and 47 would have to be tested for effective insecticidal activity. Because each variant and each fragment of each protein would have to be tested for insecticidal activity, the

differences between the two types of activities according to the claims as written is not apparent.

Among the tested proteins, some would have to have SEQ ID NO: 34 varied with conservative substitutions, some would have to have SEQ ID NO: 45 varied with conservative substitutions, and some would have to have SEQ ID NO: 47 varied with conservative substitutions. Among the tested proteins with varied SEQ ID NO: 34, the variations would have to be that any number of amino acids at a large number of different amino acid positions are conservatively substituted, and many different substituted amino acids would have to be tested at each position. This procedure would have to be repeated for variants of SEQ ID NOS: 45 and 47. Also, for each of SEQ ID NOS: 34, 45 and 47, a set of fragments would have to be prepared and tested. In each set, subsets would have to be prepared and tested in which, in the first subset, one amino acid is deleted, in the second subset two amino acids are deleted, in the third set, three amino acids are deleted, etc. For each subset of each protein, a group of proteins would have to be prepared and tested in which all possible permutations of a fixed number of missing amino acids are covered and included. For each variant protein and for each protein fragment, the insecticidal activity would have to tested against a wide variety of insects. Each experiment for insecticidal activity would have to be carried out at a range of variant protein concentrations, insects to be controlled or inhibited, and assay conditions (e.g., insect culture media- natural and artificial, temperature, location- above ground (in air) vs. below ground (in soil), etc.).

These types of experiments and data are missing from the specification. A great deal of guidance is needed to establish that any fragment or conservatively substituted

variant of SEQ ID NOS: 34, 45 or 47 has insecticidal activity because these proteins are claimed and no disclosure of such proteins is provided. Even if one such variant or fragment protein is made, by random, trial-and-error deletion or substitution and found to be functionally active (insecticidal), without a very large amount of data, such a result could not be expected with a different variant or fragment protein tested under different conditions, such as with a different insect or with a different amount of protein.

Therefore, the claims fail to satisfy the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-8, 10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims recite that the proteins in the claimed method may be substituted by conservative amino acid substitutions. Conservative amino acid substitutions are not defined in the specification, although examples of such substitutions are provided in paragraph 190. As a result, the claims are vague and indefinite, as it cannot be determined what substitutions Applicants have made to produce the proteins recited in the claimed method. Applicants may amend the claims to include the amino acid substitutions that they have made to arrive at the proteins used in the claimed method by including the substitutions of the examples in the specification. That is, the claims may be amended to recite that SEQ ID NOS: 34, 45 and 47 have conservative amino acid substitutions wherein lysine or arginine is substituted for histidine, etc. Appropriate correction is required.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 14 recites that Proteins B and C are encoded by polynucleotides that hybridize under stringent conditions to polynucleotides that are the complementary sequences of those encoding SEQ ID NOS: 45 and 47. Stringent hybridization conditions are not defined in the specification. Examples of stringent hybridization conditions are provided in paragraphs 170 and 173-177. Because stringent hybridization conditions are not defined, the claim is vague and indefinite, as it cannot be determined which hybridization conditions are used to yield the claimed polynucleotide and protein sequences. Applicants may amend the claim to include specific stringent hybridization conditions by including the conditions of the examples in the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly

owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-8, 10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morgan et al. ("Sequence analysis of insecticidal genes from *Xenorhabdus nematophilus* PMFI296," Appl Environ Microbiol 67:2062-2069, 2001) in view of Ffrench-Constant et al. (US 2004/0103455, which claims priority to US 60/425,672, filed on November 12, 2002), Duchaud et al. (WO 02/094867) and Kramer et al. (US 6,281,413). Morgan et al. disclose an insecticidal protein from *X. nematophilus* PMFI296 that has 95% sequence identity to SEQ ID NO: 34, XptA1 (see enclosed alignment, Result 1 from a search in the UniProt database, see also pp. 2063-2064 of Morgan et al.). Morgan et al. note that most related proteins to this one appear to be the TccC and TcaC proteins from P. luminescens, a distantly related organism, and that a common set of insect toxins exists in bacteria associated with IPN (insect parasitic nematodes). This common set may be the result of an ancient common ancestor or of gene exchange (see pp. 2065, 2067 and 2068).

Ffrench-Constant et al. disclose insecticidal proteins from *Photorhabdus luminescens* (see paragraphs 3-7), SEQ ID NO: 10 and 12, that have 100% sequence identity to SEQ ID NOS: 45 and 47, respectively (see enclosed alignments, Result 1 from a search in the database of published U.S. patent applications for each protein). SEQ ID NO: 10 is the protein TcdB2, which has activity equivalent to that of the protein TcdB1 (see paragraphs 9 and 22). SEQ ID NO: 12 is the protein TccC3, which has activity equivalent to that of the protein TccC2 (see paragraphs 9 and 24). TcdB and TccC2 proteins are known to enhance the toxicity of the insecticidal TcdA1 protein. Host cells expressing all three

heterologous proteins are more toxic to insects than the same host cells expressing TcdA1 alone (see paragraph 7).

Duchaud et al. (WO 02/094867) disclose an insecticidal protein, TcaC, SEQ ID NO: 3319, from *Photorhabdus luminescens* (see Abstract, p. 1, lines 10-14, and p. 359, 1st row) that has 92% sequence identity to SEQ ID NO: 45 (see enclosed alignment, Result 3 from a search in the Geneseq database).

Kramer et al. disclose an insecticidal protein from *Photorhabdus luminescens*, SEQ ID NO: 12, that has 91% sequence identity to SEQ ID NO: 47 (see enclosed alignment, Result 1 from a search in the database of issued U.S. patents). The insecticidal protein of Kramer et al. has broad-spectrum activity (see col. 2, lines 5-38, and col. 11, lines 40-64) and is encoded by orf5 of SEQ ID NO: 11 (see col. 11, lines 9-10).

The foregoing references disclose that Protein A is from the genus *Xenorhabdus* and Proteins B and C are from the genus *Photorhabdus*. It would have been obvious to one of ordinary skill in the art at the time that the invention was made to control or inhibit an insect by contacting it with a composition comprising the proteins of SEQ ID NOS: 34, 45 and 47, because the prior art discloses that a protein having at least 40% sequence identity to each of these proteins has insecticidal activity. Although the cited references do not teach this combination in one reference, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to produce an insecticidal composition comprising three proteins, each of which has at least 40% sequence identity to SEQ ID NOS: 34, 45 and 47, respectively. Each of these proteins has been individually taught in the prior art to be successful at controlling or inhibiting insects. The instant situation is amenable to the type of analysis set forth in In re

Kerkhoven,205 USPQ 1069 (CCPA 1980), wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose, as the idea of combining them flows logically from their having been individually taught in the prior art. See also MPEP 21440.06. Applying the same logic to the instant method claims, one of ordinary skill in the art would have reasonably expected to obtain insecticidal proteins with any one or with all five of the prior art proteins, including a protein that has at least 40% sequence identity to SEQ ID NO: 34, a protein that has at least 40% sequence identity to SEQ ID NO: 45 and a protein that has at least 40% sequence identity to SEQ ID NO: 47, because all of the cited proteins have been demonstrated in the prior art to be effective insecticides.

Additionally, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Ffrench-Constant et al. disclose that TccC3, which is the same protein as SEQ ID NO: 47, and TcdB2, which has the activity of TcdB proteins and is the same protein as SEQ ID NO: 45, have the additional property that they enhance the toxicity of a protein that is known to be an insecticide. It would have been obvious to one of ordinary skill in the art to add toxicity-enhancing proteins to a composition comprising an insecticidal protein to make the composition more toxic and therefore more effective. Thus, it would have been obvious to the artisan of ordinary skill to add the

proteins of SEQ ID NOS: 45 and 47 to an insecticidal composition comprising a protein having at least 40% sequence identity to SEQ ID NO: 34.

In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner, Art Unit 1653

rk/2006-02-23

Rosanne Kosson

ROBERT A. WAX
PRIMARY EXAMINER